REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, are respectfully requested in light of the remarks which follow.

Claims 4-28, 30, 35 and 68-70 are now in this application. Claims 1, 2, 3, 29, 31-34 and 36-67 have been cancelled and claims 68-70 have been added.

The acknowledgment of the claim to domestic priority under 35 U.S.C. §119(e) is noted, with appreciation.

Applicants also acknowledge, with thanks, receipt of an initialed copy of applicants' Form PTO-1449 filed May 8, 2002. A Second Information Disclosure Statement is being filed concurrently herewith.

With respect to the claim amendments, the Examiner will note that some of the changes are grammatical in nature or address specific §112 issues she has raised. Other amendments are simply intended to place the claims in better form. The additions made to claims 9, 11 and 13 are based on the specification, in particular, Example 2. As to the new claims, claim 68 represents a combination of the features of original claims 1, 2 and 3, with clarification. Claim 69 is drawn to subject matter previously claimed in original claim 7, while claim 70 is drawn to subject matter previously claimed in original claim 10. No new matter has been added.

In response to the objection to claim 18 as containing a typographical error, claim 18 has been amended to reflect the correct spelling of "plasticizer".

In response to the rejection of claims 2, 4-13, 37, 40, 43 and 64-65 under 35 U.S.C. §112, second paragraph, it is submitted that the claims as amended overcome or obviate the rejection.

Specifically, claim 67, which represents a combination of original claims 1, 2 and 3, does not contain the wording "which is further provided an oily matrix" which the Examiner considered indefinite. Therefore, this rejection of claim 2 and its dependent claims 5-13 has been obviated.

Next, the wording "depending on assay, . . ." in claim 4 has been deleted, while claim 37 has been deleted in its entirety. Consequently, this wording which the Examiner regarded as superfluous no longer appears in the claims, rendering the rejection moot in this regard.

Further, with respect to the recitation of a broad recitation with a narrow recitation in claims 7, 10, 40 and 43, the Examiner will note that each of claims 7 and 10 has been amended to reflect only the broad recitations, while new claims 69 and 70 have been added to cover the original narrow recitations. This amendment clearly overcomes the rejection of claims 7 and 10. As to claims 40 and 43, these claims have been cancelled, thus obviating the §112 rejection with respect thereto.

Claims 64 and 65 have been rejected as using terms which have no antecedent basis. These claims have been cancelled, obviating the §112 rejection.

In view of the foregoing, it is believed that no aspect of the §112, second paragraph, rejection can be maintained against the claims now in this application.

Claims 1-34 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Adusumilli et al (U.S.P. 5,595,758) in view of Zappia et al (U.S.P. 4,764,603) and Fiecchi (U.S.P. 3,954,726). Applicants submit that all of the claims now in this application are free of this rejection.

Adusumilli et al describe a soft-shelled gelatin capsule which contains particles in a liquid vehicle. Adusumilli et al do not describe such capsules containing an SAMe salt. Adusumilli et al do not address the encapsulation of difficult-to-encapsulate materials. As noted in applicants' specification, encapsulation of SAMe is not as easy as theorized. The first problem is the hygroscopic nature and low pH of SAMe, which do not permit easy encapsulation because the initial high water content of the gelatin shell has an adverse effect on the compound. The second problem is that if the table is enteric coated, the coating has to be optimized for the desired availability of SAMe at the target site, i.e. the anterior part of the intestine.

It has not been previously envisaged to coat SAMe with soft gelatin film because such encapsulation would be expected to cause deterioration of SAMe. However, applicants have surprisingly found that such encapsulation provides enhanced shelf-life of SAMe as well as 95% protection from degradation, employing S-adenosylmethionine disulphate tosylate and monosulphate tosylate salts.

Zappia et al describe very special stable salts of SAMe with polyanions such as polyphosphates. These are not the salts encompassed by applicants' claims. Zappia et al's salts have very different properties from SAMe and their patent does not teach how to encapsulate SAMe and other salts. Zappia et al's salts were in fact devised to avoid

SAMe's degradation problem. Moreover, it appears that Zappia et al's capsules are hard capsules filled with solids, not capsules containing a lipid suspension in a soft gelatin film.

Fiecchi describes double salts of SAMe with sulphuric acid and p-toluenesulphonic acid but does not address how to make soft gelatin capsules. The capsules disclosed in column 15, like those of Zappia et al, appear to be hard capsules, not soft gelatin capsules as described and claimed herein.

As noted in the instant specification (page 12, for example), the instant capsules are stable and durable and can be used for at least two years from the date of manufacture. SAMe tablets often soften and discolor, sometimes even with leaching of the active moiety under conditions for which the instant soft gelatin capsules do not show such degradation (25°C. and ambient relative humidity). As further noted in the specification, the tablet dosage form generally incorporates the active moiety in solid matrix, which may not be a favorable condition for better absorption and availability of the active moiety (SAMe) in the body. The same can be said of a solid capsule as shown by Zappia et al and Fiecchi.

Moreover, it is submitted that the disclosure of Adusumilli et al in column 6, lines 43-44, which teaches that their soft gelatin capsule dosage form can enhance the bioavailability of water insoluble highly lipophilic drug substances, does not suggest that SAMe would be useful in Adusumilli et al's capsules. SAMe is a highly temperature-sensitive and moisture-sensitive material and it is these qualities which particularly impact on its formulation. Adusumilli et al teach nothing about encapsulating materials which are highly hygroscopic and temperature-sensitive as well as lipophilic. Therefore, the art is absent any motivation to combine the references, for Adusumilli et al do not address the

soft gelatin encapsulation of a highly hygroscopic and temperature-sensitive material such as SAMe.

For at least the reasons given above, the cited references, separately or in combination, do not teach or suggest the subject matter of applicants' amended claims.

Claims 35-67 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over Adusumilli et al in view of Matthews et al (U.S.P. 4,816,259), Zappia et al and Fiecchi. Of these claims, claim 35 remains in the application, in amended form. As with the other claims now in the application, claim 35 is now limited to particular SAMe salts, i.e. the SAMe monosulphate tosylate salt and the SAMe disulphate tosylate salt. It is submitted that this claim, too, is free of the record rejection.

The Adusumilli et al, Zappia et al and Fiecchi patents have been discussed above. As already noted, Zappia et al and Fiecchi do not suggest enteric-coated soft gelatin capsules of the salts here named, indeed they do not appear to disclose soft gelatin capsules of any salts. Adusumilli et al teach soft gelatin capsules, but do not suggest SAMe for encapsulation; moreover, Adusumilli et al do not suggest how to encapsulate a highly hygroscopic, temperature-sensitive material such as SAMe. Matthews et al do not fill the gap with respect to the claimed process. Applicants' process begins with coating the SAMe salt (the monosulphate tosylate or disulphate tosylate) with a lipophilic material to obtain granules, then mixes the granules with an oily matrix, antioxidants and preservatives to form a lipid suspension, disposes the lipid suspension in a soft gelatin film and then coats the soft gelatin film with an enteric coating to give the final product. Matthews et al appear to provide a finished coated soft gelatin capsule shell for encapsulating solid, semi-solid or

liquid dosage forms. Hard gelatin capsules are also described. Matthews et al certainly do not suggest encapsulation of SAMe or a salt thereof. Moreover, Matthews et al suggest that their process include drying the capsules prior to coating by tumbling with warm air, which should be approximately 75°C, passing over the capsules. Since SAMe is temperature-sensitive, it would not appear to one of ordinary skill to be desirable to subject SAMe to such a temperature.

It is apparent from the foregoing that none of the references suggest the instantly claimed invention. Neither Matthews et al nor Adusumilli et al address the particular problems (hygroscopicity and temperature sensitivity) of SAMe or its salts which soft gelatin encapsulation would need to address. Likewise, Zappia et al and Fiecchi do not provide soft gelatin capsules of the SAMe salts specified in the instant claims, or of any SAMe salts.

In view of the above, it is submitted that the claims as amended hereinabove are free of all record rejections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26,254

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620